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Signed Andrew Gersey

Dated **14 June 2000**

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P01/7700 0.00-0003235.9

Your reference
PCS10370 JWM-PROV2

0003235.9

11 FEB 2000

Notes
Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071-438 4700).

Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.

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The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

1 Title of invention

1 Please give the title of the invention

TREATMENT OF PULMONARY HYPERTENSION

2 Applicant's details

☑ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name
PFIZER LIMITED

Country *(and State of incorporation, if appropriate)*
UNITED KINGDOM

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases,** please give the following details:

Address
RAMSGATE ROAD
SANDWICH
KENT

UK postcode CT13 9NJ
(if applicable)

Country UNITED KINGDOM

ADP number *(if known)* 6892673001

2d, 2e and 2f:
If there are further applicants please provide details on a separate sheet of paper.

☐ **Second applicant (if any)**

2d If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2f **In all cases,** please give the following details:

Address

UK postcode
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Country

ADP number
(if known)

3
An address for service in the United Kingdom must be supplied.

Please mark correct box

3 Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] ➡ ***go to 3b***

⬇ ***Please give details below***

Agent's name
J. W. MOORE
Agent's address
PFIZER LIMITED
RAMSGATE ROAD
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Agent's ADP number 56 293 24001

3b:
If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

Address

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Daytime telephone number*(if available)*

ADP number
(if known)

4 Reference number

4 Agent's or applicant's reference number *(if applicable)* PCS10370 JWM-PROV2

5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ *go to 6*

⬇ *please give details below*

☐ number of earlier application or patent number

☐ filing date *(day month year)*

☐ and the Section of the Patents Act 1977 under which you are claiming:

Please mark correct box

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

6 Declaration of priority

6

If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day,month,year)*

7

The answer must be 'No' if:
- *any applicant is not an inventor*
- *there is an inventor who is not an applicant, or*
- *any applicant is a corporate body.*

8

Please supply duplicates of claim(s), abstract, description and drawing(s).

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark the correct box

Yes [ ] No [X] ➡

A statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77			
Claim(s)	1	Description	7
Abstract		Drawing(s)	

8b Which of the following documents also accompanies the application?

Please mark correct box(es)

Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 - Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 - Preliminary Examination/Search	
Patents Form 10/77 - Request for Substantive Examination	

9

You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

Please sign here ➡

9 Request

I/We request the grant of a patent on the basis of this application.

Signed [signature] Date 02/02/2000 *(day month year)*

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Please return the completed form, attachments and duplicates where requested, together with the prescribed fee to:

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The Patent Office
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S10370JWM-PROV2

TREATMENT OF PULMONARY HYPERTENSION

This invention relates to the use of the compound sildenafil, for the treatment of pulmonary hypertension.

Pulmonary hypertension is a pathological condition in which the pulmonary artery pressure rises above normal levels and may cause sequelae of haemodynamic changes that can become life threatening. Symptoms of pulmonary hypertension include shortness of breath with minimal exertion, fatigue, dizzy spells and fainting. When pulmonary hypertension occurs in the absence of a known cause, it is referred to as primary pulmonary hypertension. Primary pulmonary hypertension is rare occurring in about 2 per million people worldwide.

Secondary pulmonary hypertension is much more common occurring as a result of other medical conditions, including congestive heart failure, chronic hypoxic lung disorder, including chronic obstructive pulmonary disease, inflammatory or collagen vascular diseases such as scleroderma and systemic lupus erythematosus, congenital heart diseases associated with left to right shunting and pulmonary thromboembolism.

Sildenafil (Viagra ®) is an orally-active, potent and selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5) which is the predominant PDE isoenzyme in human corpora cavernosa. Consequently, it has been shown to be effective in the treatment of male erectile dysfunction. PDE5 is selectively abundant in the pulmonary vasculature compared to systemic vessels. Sildenafil increases intracellular concentrations of nitric oxide (NO) derived cGMP, thereby enhancing the effect of NO, and thus has potential to reverse metabolic and vascular defects in subjects with pulmonary hypertension.

It is known that inhaled NO stimulates the production of cGMP in pulmonary vascular smooth muscle cells resulting in selective pulmonary vasodilation. Recently, it has been observed that administration of inhaled NO to subjects with severe pulmonary hypertension resulted in significant decreases in pulmonary artery pressure and pulmonary vascular resistance without concomitant systemic hypotension. However the dose of inhaled NO is potentially limited by the formation of nitrogen dioxide, peroxynitrite or other toxic by-products. PDE5 is selectively abundant in the pulmonary vasculature in comparison to the systemic vessels and it has been observed that PDE5 is upregulated in pathological conditions leading to increase in pulmonary pressure. Sildenafil as a PDE5 inhibitor is expected to increase the level of cGMP and thus prolong the beneficial effect of the reduction of pulmonary blood pressure caused by NO with little effect on systemic blood pressure.

The use of phosphodiesterase inhibitors administered endotracheally or endobronchially (i.e. by inhalation) to treat pulmonary hypertension has been described in WO95/09636 but the compounds employed were neither particularly potent nor selective cGMP PDE inhibitors.

Sildenafil (5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1,6-dihydro-1-methyl-3-propylpyrazolo[4,3-*d*]pyrimidin-7-one) and its preparation are described in European patent 0463756.

Thus according to the present invention we provide a method of treating a patient with pulmonary hypertension which comprises treating the patient with an effective amount of sildenafil or a pharmaceutical composition thereof.

The invention also provides for the use of sildenafil for the manufacture of a composition for treating pulmonary hypertension.

For use in the present invention sildenafil is preferably administered as a pharmaceutical composition. Thus, the compound can be administered in any conventional oral, parenteral, or transdermal dosage form, usually with a pharmaceutically acceptable carrier or diluent. Sildenafil is preferably employed in the form of its citrate salt but other pharmaceutically acceptable salts may also be used.

For oral administration a pharmaceutical composition can take the form of a solution, suspension, tablet, pill, capsule, powder or the like. Tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as potato or tapioca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often used for tabletting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the compounds can be combined with various sweetening agents, flavoring agents, colouring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

Methods of preparing such pharmaceutical compositions with a certain amount of active ingredient are well known to those skilled in this art, or may be determined by reference to literature precedents.

Sildenafil may also be administered as an inhaled formulation and this may have advantages in delivering the active compound directly to the lung area. For this embodiment the aerosol particle size is preferably between 0.5 micrometers and 5 micrometers. The aerosol is conveniently generated by a conventional nebuliser or atomiser.

Solutions of the active ingredient for use in such inhalers are prepared by conventional methods, typically by dissolving the active ingredient in water which is preferably buffered to pH 3-8, more preferably pH 4 to 7 using standard buffer systems such as citrate, lactate or phosphate buffers to control the pH. Ethanol may also be added at a concentration of up to 30% to improve aerosolisation of the formulation. Additional stabilisers may be required to improve chemical stability of the formulations; ie anti-oxidants, such as sodium metabisulphite, sodium bisulphite or tocopherol, or metal chelators such as ethylenediaminetetraacetic acid.

Single unit-dose spray can be prepared aseptically or terminally sterilised to produce a sterile final product. Alternative, multi dose metered nebulisers or atomisers can be used.

Flavourings, perfumes and humectants may also be added to improve the patient acceptability of the formulation. Solubility enhancers eg caffeine can be added to improve solubility of the active drug.

One particular and preferred formulation comprises an aqueous formulation of sildenafil mesylate for use in an aerosol nebuliser or atomiser to provide a dose of from 5 to 20mgs of sildenafil mesylate per dose.

Alternatively the drug may be administered as a micronised powder. For this application the active drug is preferably blended with a suitable carrier, eg lactose, and the formulation micronised to provide a particle size distribution in the range 0.1 to 5 micrometres and preferably less than 1 micrometre. The powder can be placed in hard gelatin capsules for use in conjunction with a conventional dry powder inhalation device.

The inhaled formulations described above should deliver a dose of sildenafil of from 1 to 50mg, more preferably from 5 to 20mgs per dose. The exact dose of sildenafil administered will, however, differ depending on the subject being treated, on the severity of the condition, on the manner of administration and on the judgment of the prescribing physician. Thus, because of patient-to-patient variability, the dosages given below are a guideline only and the physician may adjust doses of the compounds to achieve the treatment that the physician considers appropriate for the patient. In considering the degree of treatment desired, the physician must balance a variety of factors such as the age of the patient and the presence of other diseases or conditions (e.g. cardiovascular disease). In general, the compound will be administered in a range of from 5 to 125 mg per day, more preferably 25-100 mg per day.

Sildenafil may also be administered in conjunction with the administration of nitric oxide to treat pulmonary hypertension.

In addition to treatment of adult patients , a further application of the invention is in the treatment of very young children born with congenital heart disease. Sildenafil can be used to treat pulmonary hypertension in such subjects and can thus delay the immediate need for surgery until the patient is better able to withstand the trauma of surgery. Sildenafil can also be used to treat children who have pulmonary hypertension post operatively or due to respiratory distress syndrome or neonatal hypoxia.

Examples of particular formulations are included hereinafter to further illustrate the invention.

EXAMPLE 1

DRY POWDER FORMULATION FOR INHALATION

A dry powder formulation of sildenafil citrate was prepared by blending micronised drug (1 g) with lactose suitable for inhalation use, e.g. Pharmatose (trade mark), 325 mesh, (10 g) to provide a blend having a particle size distribution in the range 1 to 5 micrometres. The product was filled into hard gelatin capsules (150 mg) for use with a commercial dry powder inhalation device.

Similar formulations are prepared of sildenafil mesylate and sildenafil free base.

EXAMPLE 2

SOLUTION FORMULATION FOR INHALATION

A solution was prepared of sildenafil mesylate having the following composition:

Sildenafil mesylate	10g
Sodium dihydrogen phosphate	0.69g
Distilled water	90ml
Ethanol	10ml

The solution was stirred to dissolve the ingredients and the pH adjusted to 4.2 by the addition of 1M sodium hydroxide solution. The solution was sterilised by ultrafiltration or autoclave and the cooled solution was aseptically filled into dark bottles for use with a commercial nebuliser or atomiser providing a unit dose of 10mg of active drug per inhalation.

EXAMPLE 3

Preparation of 5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl] - 1, 6-dihydro-1-methyl- 3-propylpyrazolo [4,3-d]pyrimidin-7-one) methanesulphonate salt (sildenafil mesylate)

5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl] - 1, 6-dihydro- 1-methyl- 3-propylpyrazolo [4,3-d]pyrimidin-7-one)[1] (100g, 0.21 mol) was dissolved in boiling acetone (3000 ml). Methanesulphonic acid (14.9 ml, 0.23 mol) was added to the hot acetone solution. Within 10 seconds a precipitate formed. The mixture was allowed to cool and granulate for 48 hours. The title product was collected by filtration and dried in vacuum to give a white crystalline solid (116.0g, 96.8%), m.p. 272-274ºC.

Found: C, 48.33; H, 5.99; N, 14.68. $C_{23}H_{34}N_6O_7S_2$ requires C, 48.41; H, 6.00; N, 14.73 % δ (CD_3SOCD_3)[2] 0.92 (3H, t), 1.33 (3H, t), 1.73 (2H, heptet), 2.29 (3H,s), 2.77 (2H, t), 2.79 (3H, s), 3.16 (2H, br), 3.3-3.57 (4H, br), 3.8 (2H, br), 4.16 (3H, s), 4.20(2H, q), 7.4 (1H, d), 7.88 (1H, dd), 7.90 (1H, s), 9.44 (1H, br).

CLAIMS

1. A method of treating a patient suffering from pulmonary hypertension which comprises treating said patient with an effective amount of sildenafil or a pharmaceutical composition thereof.

2. The use of sildenafil for the manufacture of a pharmaceutical composition for the treatment of pulmonary hypertension.

3. A pharmaceutical formulation of sildenafil or a pharmaceutically acceptable salt thereof in a form adapted for inhaled administration for delivery to the lung.

4. A pharmaceutical formulation as claimed in claim 3 which comprises sildenfil mesylate in a formulation for inhaled administration with an aerosol nubuliser or atomiser.